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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/332,063	06/14/99	HOLMGREN L	3362-0101P

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EXAMINER	
HARRIS, A	
ART UNIT	**PAPER NUMBER**
1642	11

DATE MAILED: 02/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/332,063	H Imgreen & Troyan vsky
Examiner	**Group Art Unit**
Alana M. Harris, Ph. D.	1642

☒ Responsive to communication(s) filed on *Jan 4, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-30* is/are pending in the applicat

Of the above, claim(s) *9-27* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8 and 28-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *9*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

1. Applicant's election with traverse of Groups I (claims 1-8 and 28-30) in Paper No. 10 (filed January 4, 2000) is acknowledged. The traversal is on the ground(s) that the search of Group I, drawn to human angiogenesis-associated proteins and peptides and Group IV, drawn to a screening method utilizing the said proteins are interrelated. This is not found persuasive. The claims of each Group are classified differently, necessitating different searches in the U.S. Patent shoes. Classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Further, Group IV involves various method steps, which require additional searching.

The requirement is still deemed proper and is therefore made FINAL.

However, the policies set forth in the Commissioner's Notice of February 28, 1996 published on March 26, 1996 at 1184 O.G. 86 will be followed. Method claims limited to the scope of the allowable product claims will be rejoined and examined at the time the product claims are indicated as being allowable.

2. Claims 1-30 are pending.

Claims 9-27, drawn to non-elected inventions are withdrawn from examination.

Claims 1-8 and 28-30 are examined on the merits.

Priority

3. Sequences identical to SEQ. ID. NO. 2, SEQ. ID. NO. 3 and SEQ. ID. NO. 4 are not found in the Provisional Application #60/089,266 (filed 6/15/98). However, identical sequences were found in the Provisional Application #60/114,386 (filed 12/29/98). Thus, for the application of the art to claims (3-8) reciting any of these sequences priority is granted to 12/29/98.

Claims 1, 2 and 28-30 are granted the priority date of the Provisional Application #60/089,266 (filed 6/15/98).

Drawings

4. The drawings are objected to because of reasons cited on attached form PTO 948 completed by draftsman. Correction is required.

Specification

5. The disclosure is objected to because of the following informalities: the brief description of the figures lack a separate brief description of Figures 1c, Figure 2a and Figure 2b.

Appropriate correction is required.

Claim Objections

6. Claims 28-30 are objected to under 37 CFR 1.75© as being in improper dependent form. See MPEP § 608.01(n). If the recitation 'any one of claims 1 to 8 and 26" is interpreted as any

one of claims 1 to 8 always paired with claim 26, claims 28-30 do not properly depend from multiple claims in the alternative form only.

Claim 28 is improperly multiple dependent because it depends from another multiple dependent claim (claims 3-6), which depend from claim 3.

Claim 28 does not further limit claims 1-8 by merely reciting an intended use.

Claim 28 is an improper dependent claim to the extent that it depends from claim 26. Claim 26 is drawn to a different statutory class of invention to a "use", not to a peptide.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 1-8 and 28-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

a. Claim 3 is broadly drawn to "the protein of claim 1 or 2 comprising an amino acid sequence having at least approximately 80% sequence homology, preferably approximately 90% sequence homology, more preferably approximately 95% sequence homology and most preferably

approximately 98% sequence homology to SEQ. ID. Nos. 2, 3 or 4". The specification while being enabling for the amino acid sequences 2, 3 and 4, which are designated as the protein(s) "ABP-1" and amino acid variants of ABP-1 that are defined by its ability to bind a fragment of plasminogen, preferably the first four Kringle domains, does not provide enablement for the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar biological activity requires a (1) knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectantly intolerant to modification), and (2) detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation. Thus, the claimed protein of claim 1 or 2 comprising an amino sequence having at least approximately 80% sequence homology, preferably approximately 90% sequence homology, more preferably approximately 95% sequence homology and most preferably approximately 98% sequence homology to SEQ. ID. No:2, 3 or 4 could be a number of variant proteins. Likewise, claims 7 and 8 are broadly drawn to "an amino acid sequence comprising at least 5 contiguous amino acid residues of SEQ. ID. NO. 2" and "an amino acid sequence comprising at least 10 contiguous amino acid residues of SEQ. ID. NO. 2",

respectively. Again, this is a vast collection of polypeptides and the specification provides inadequate instruction to allow one of skill in the art to make and use said polypeptides with a reasonable expectation of success and without undue experimentation.

While the specification teaches the specified SEQ. ID. No: 2, 3 and 4 and how to use only proteins which possess anti-angiogenic activity, the specification provides no direction or guidance or working examples of how to use an enormous number of variant proteins encompassed by the claims as to functional or physical properties to aid in the identification and use of the broadly claimed proteins. Any number of proteins could fit the parameters of Applicant's claim, thus there would be literally infinite combinations of possible proteins that would and would not be successfully applied to Applicant's invention. As discussed in "Bio, Critical Synergy: The Biotechnology Industry and Intellectual Property Protection" (1994), each individual protein is art recognized to be very empirical, with conditions for isolating, and thus using any given protein, greatly divergent from those of other proteins (see p. 101, 103 and 104).

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin, Schwartz et al. (Proc. Natl. Acad. Sci. USA Vol 84:6408-6411, 1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase Lin et al. (Biochemistry USA 14:1559-1563, 1975). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the

protein. Even if one has the correct amino acid sequence, a skilled practitioner would not be able to predict the level of expression of the resulting synthetic DNA sequence.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonable correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement. In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of derivatives encompassed in the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

b. Claim 30 is broadly drawn to "a pharmaceutical composition comprising a substantially purified human tumor-associated antigen". The specification while being enabling for a composition comprising an isolated human angiogenesis-associated protein of claim 1 and a pharmaceutically acceptable carrier, does not reasonably provide enablement for a "pharmaceutical composition" comprising these same components. Claims drawn to "pharmaceutical compositions" are broadly interpreted to read on compositions effective for use as *in vivo* human therapeutics. The proteins, peptides or compounds of the invention are completely uncharacterized functionally. The mere fact that these proteins are "angiogenesis'associated" is not sufficient to establish that they do or will play a role in the pathology or etiology of angiogenic disorders and/or cancer. In the absence of an established role of the proteins, peptides or compounds in the aforementioned diseased states it is impossible to

predict what if any therapeutic effect the administration of the proteins, peptides or compounds as a medicament would have for the treatment of angiogenic disorders and cancer. The selection and development of such human therapeutics is art known to be highly unpredictable. The specification exemplifies no examples of the effective use of the effective use of the polypeptide as a pharmacological agent and no such uses are art known. The specification lists "the molecules used as medicaments according to the invention may be anyone of the described peptides, polypeptides, proteins or antibodies as well as **any novel substance** identified...". This reasonably conjures the question as to how selective must these molecules be before subscribing them to the intended use of the medicament? Could any novel substance that was identified in a screening method be selective and specific in the application of treatment regarding an angiogenic disorder or cancer? Those skilled in the art cannot rely on this information to utilize any novel substance as medicament. Therefore, due to the unpredictability of therapeutics and the absence of any evidence concerning the effectiveness of the claimed pharmaceutical composition as a pharmacological agent, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use with a reasonable expectation of success, the invention commensurate in scope with this claim. The applicant is advised to amend the claim to delete the recitation of "pharmaceutical".

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-4 and 28-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. The recitation "angiogenesis-associated protein" in claim 1 is vague and indefinite. It is unclear what actually are defining features of an 'associated' angiogenesis protein.

b. The identity of "kringle domains 1 to 4 of plasminogen" in claim 2 is unclear. The applicant is advised to amend the claim to include additional identifying characteristics such as identifying SEQ. ID. numbers.

c. Claim 3 is vague and indefinite in the recitation "having **at least** 80% sequence homology, **preferably** approximately 90% sequence homology, **more preferably** approximately 955 sequence homology and **most preferably** approximately 98% sequence homology to SEQ. ID. NOs. 2, 3 or 4." It is unclear how these various preferences influence the metes and bounds of the claimed proteins having "at least approximately 80% sequence homology" to SEQ. ID. NOs. 2, 3 or 4.

d. Claim 28 is vague and indefinite in the recitation "for use as a medicament." It is unclear how the intended use of the claimed proteins, peptides or compounds further limits these products.

e. The recitation "compounds" in claims 28 and 29 lack proper antecedent bases in any of claims 1-8 or 26.

f. Claims 29-30 are vague and indefinite in their recitation of non-elected claim 26.

g. Claims 28-30 are vague and indefinite in the recitation "any one of the claims 1-8 and 26." Is this to be interpreted as one claim selected from claims 1-8 or 26 or as two claims **or** any of claims 1-8 paired with claim 26?

c. The recitation "a medicament" is vague and indefinite in claims 28 and 29. It is not clear if the intended use is directed to a product or a method of treatment.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claim 29 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. It is not clear whether "use" is a process, manufacture, composition of matter or some other item that is not one of the statutory categories of invention. It is noted that method claims must recite positive method steps.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

14. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Petersen et al. (Journal of Biological Chemistry 205(11):6104-6111, 1990). Petersen et al. disclose fibrin, a human angiogenesis-associated protein capable of binding an N-terminal fragment of plasminogen, wherein the N-terminal fragment of plasminogen is constituted by the kringle domains 1 to 4 of plasminogen, the same as that claimed.

15. Claims 1, 2 and 28-30 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent # 5,679,350 (filed May 8, 1996). U.S. Patent #5,679,350 discloses two human angiogenesis-associated proteins, urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) that are capable of binding a N-terminal fragment of plasminogen, wherein the N-terminal fragment of plasminogen is constituted by the kringle domains 1 to 4 of plasminogen, the same as that claimed (claims 1 and 2).

U.S. Patent #5,679,350 also discloses that uPA and tPA proteins are coupled with a carrier contained within a medicament directed towards an angiogenesis-related disease or disorder such as cancer (claims 28-30).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris whose telephone number is (703) 306-5880. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Alana M. Harris, Ph.D.
Patent Examiner, Group 1642
February 14, 2000

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER